The Oncologist®

Symptom Management and Supportive Care

Aiming for a Better Understanding and Management of Cancer-Related Fatigue

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Fatigue • Drug therapy • Questionnaires • Neoplasms • Methylphenidate • Modafinil

ABSTRACT

Cancer-related fatigue (CRF) is a serious symptom of patients with cancer and deteriorates their daily quality of life. Whereas fatigue is a common problem in the general population, with a prevalence of about 30%, up to 99% of patients with cancer have fatigue of more intense severity. CRF is directly related to the biology of cancer, but it can also be caused by anticancer treatment. We reviewed current evidence about the potential pathophysiological mechanisms causing CRF. Clinical methods to determine the presence and severity of CRF and potential treatment options to reduce CRF will be discussed. After reading this review, the reader will have knowledge of the current understanding of CRF and will be able to give evidence-based advice to patients with CRF. ***The Oncologist*** 2013;18:1135–1143

Implications for Practice: Cancer-related fatigue (CRF) is a common problem in patients with cancer and has a major impact on quality of life. The causes of CRF are multifactorial and not fully understood. To get a better insight into the underlying mechanisms and the potential treatment possibilities of CRF, we provide an overview of currently available literature on this subject. Because current treatment options other than antitumor therapy for some of the patients are scarce and only directed at symptoms, further investigation of CRF is warranted to develop rational treatment options.

INTRODUCTION

Cancer-related fatigue (CRF) is a frequently reported, deteriorating complaint in patients with cancer that has a major influence on their daily quality of life. CRF is described as a subjective feeling of tiredness, weakness, or lack of energy that influences daily activities and quality of life. In healthy people, fatigue is a functional and protective response to physical or psychological stress. In patients with cancer, fatigue has lost its protective function and does not improve after resting [1, 2]. The National Comprehensive Cancer Network (NCCN) defined CRF as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [3]. Others have proposed slightly different definitions, including the Fatigue Coalition. They stated that fatigue needs to be disproportionate to recent activities, sufficiently severe to have an impact on daily life, and the symptoms should be a direct consequence of cancer or cancer therapy [4, 5].

CRF is sometimes described as part of a cluster of symptoms together with anorexia, depression, and/or pain [6]. However, this is done mainly by cluster analysis of symptoms mentioned in literature, and clinical relevance has not yet been proven [6]. It has been proposed that CRF is a symptom of depression, but treatment with antidepressants decreases depression while CRF remains unaffected [7, 8].

Epidemiology

Fatigue is a common problem in the general population. During surveys among patients visiting general practitioners, 28% reported fatigue [9–11]. CRF has a prevalence of 15% to 99% in patients with cancer, depending on methods used for measuring fatigue and patient group characteristics [4, 12–16]. Mendoza et al. reported that healthy controls consistently rate the severity of their fatigue lower than patients with cancer [17].

Measuring Cancer-Related Fatigue

Some aspects of CRF can be measured by muscle performance tests. However, to get a more comprehensive measurement of CRF, self-report questionnaires can be used [14, 18, 19]. Forty-three questionnaires (with 55 different names) have been found that were used for measuring CRF and that are available in English [5, 12, 17–56].

The most established questionnaires for patients with cancer are the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) fatigue subscale, the Functional Assessment of Cancer Therapy for Fatigue (FACT-F), and the Fatigue Questionnaire (FQ) (supple-

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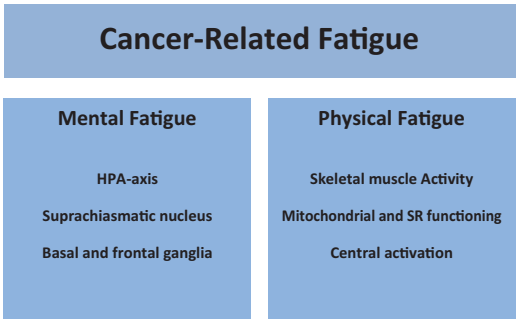

Figure 1. Pathophysiology of cancer-related fatigue. Cancer-related fatigue can be divided into mental and physical fatigue. Mental fatigue is mediated by the suprachiasmatic nucleus that controls the 24-hour circadian rhythm under the influence of the hypothalamic pituitary adrenal axis and by decreased perfusion of basal and frontal ganglia. Physical fatigue might be the result of impaired skeletal muscle activity resulting from central activation failure and changes in mitochondrial and sarcoplasmic reticulum functioning.

Abbreviations: HPA, hypothalamic pituitary adrenal; SR, sarcoplasmic reticulum.

mental online Appendix 1) [57]. These questionnaires have been validated for their internal consistency, test-retest reliability, and sensitivity to change in more than 5,000 patients. The EORTC-QLQ-C30 fatigue subscale is a three-item questionnaire that can be used for a quick measurement of fatigue. The FACT-F is a 13-item questionnaire containing questions about the level of fatigue and the consequences of fatigue in the past week. The FQ is an 11-item questionnaire with two subscales: physical and mental fatigue. The FQ focuses on the way the patient feels at that particular moment and can therefore be used on a daily basis. All three questionnaires have shown sensitivity to change over time, but minimal clinically relevant differences are not yet known. Another questionnaire that has perhaps even better psychometric qualities is the Brief Fatigue Inventory, which has nine items [12, 17, 20]. This questionnaire has been validated in approximately 1,700 patients, most of whom were non-English speaking [54].

Because of the burden a questionnaire can place on patients with fatigue, questionnaires should be easily understood and require minimum completion time. Studies of patients with CRF should, therefore, report completion rates of the questionnaires, because low completion rates may occur in patients with the highest fatigue levels.

In the clinical setting, most patients are asked to rate their fatigue on a Rhoten Fatigue Scale, which is a numerical rating scale that goes from 0 to 10, with 4 or higher as a cut-off point to take further action [3, 12, 20, 46]. This scale can, however, only be used as a screening instrument. For the follow-up of patients treated for CRF, the FACT-F can be used for its excellent psychometric qualities. For follow-up on a daily basis, the FQ would be the best questionnaire.

Pathophysiology

The pathophysiological mechanism causing CRF has not yet been clarified, but several studies provide circumstantial evidence of factors that might be involved. A summary of these factors is below and is shown in Figure 1.

Physical Fatigue

In several animal studies, activation of vagal afferent nerves caused reflex inhibition of skeletal muscle activity [58]. This reduced skeletal muscle activity might result in a feeling of general weakness in humans, which can be perceived as fatigue [58]. Cancer and cancer treatment can trigger a peripheral release of neuroactive agents, such as serotonin, several cytokines, and prostaglandins, which activate vagal afferent nerves [59–61].

In addition, tumor activity, cancer treatment, and/or cachexia alter skeletal muscle metabolism, which results in dysfunction of the sarcoplasmic reticulum, causing increased intracellular calcium levels and impairment of adenosine triphosphate (ATP) generation by the mitochondria during muscle contraction [62]. In addition to this altered metabolism, anemia and nutritional deficiencies can hamper the supply of nutrients needed for ATP generation. This potential mechanism of CRF was initially supported by a randomized clinical trial in which patients with lung cancer received infusions of ATP and showed improved muscle strength and reduced fatigue [63]. However, these results could not be confirmed in a subsequent trial by Beijer et al. and therefore should be taken with caution [64].

Kisiel-Sajewicz et al. have recently studied muscle contractile properties of patients with CRF compared with those of healthy controls. This study showed that the patients with fatigue failed earlier in motor tasks, but that this is not associated with changes in contractile properties. This lack of contractile impairment implicates a central activation failure [18].

Mental Fatigue

Mental fatigue can be triggered by the basal ganglia and the suprachiasmatic nucleus. The basal ganglia influence movement and are involved in motivation. Capuron et al. showed in a study with patients receiving interferon (IFN) treatment for stage III–IV melanoma that higher fatigue scores correlated with increased activity levels of the basal ganglia and the cerebellum [65]. Previously, it was shown that patients with depletion of dopamine in these areas also showed increased activity on positron emission tomography, possibly because of increased oscillatory burst activity [66]. In addition, the blood flow toward the basal ganglia seems to be influenced by cytokines, as shown in patients with multiple sclerosis treated with IFN [67]. The basal ganglia may also play a role in CRF, because many patients with CRF have higher levels of cytokines such as IFN, but to date no trial has been performed in patients with cancer that showed evidence for this hypothesis.

Suprachiasmatic Nucleus

The suprachiasmatic nucleus is part of the hypothalamus and regulates the 24-hour circadian rhythm through the release of melatonin and daily cortisol curves. Disruption of this 24-hour circadian rhythm has an effect on sleep patterns and sleep quality [59, 68]. The suprachiasmatic nucleus is sensitive to the amount of daylight a person receives, but can also be influenced by specific tumor-derived peptides, such as epidermal growth factor or changes in serotonin and cortisol levels [59, 69, 70].

Cortisol and serotonin influence the function of the suprachiasmatic nucleus as part of a complex signaling pathway, which has many feedback loops. Cytokines, especially interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, influence nearly every step in this pathway. Cortisol activates

glucocorticoid cell membrane receptors of the suprachiasmatic nucleus [71]. The activity level of glucocorticoid receptors can be influenced by TNF-α. Downstream of the glucocorticoid receptors NFκB regulates the production of cytokines such as IL-2, IFN-α and TNF-α. The influence of TNF-α on the glucocorticoid receptors can result in a positive feedback loop and a continuous production of cytokines [72, 73], which might result in deregulation of the 24-hour circadian rhythm. Supporting this deregulation at the level of the suprachiasmatic nucleus is the change in the cortisol curve in patients with CRF, as described by Bower et al [74]. Cortisol levels follow a daily curve, with a peak in the early morning and a down slope during the day. Bower et al. have found that breast cancer survivors who have fatigue have a more flattened cortisol slope throughout the day and a significantly elevated cortisol level in the late evening compared with breast cancer survivors without fatigue [74].

Serotonin

Serotonin and its receptors influence each other and the hypothalamic pituitary adrenal (HPA) axis. Serotonin (5-hydroxy tryptophan [5-HT]) is made in the presynaptic neuron from tryptophan. Its production is regulated by indolamine 2,3 dioxygenase, which breaks down tryptophan into kynurenine. The activity of indolamine 2,3 dioxygenase is influenced by cytokines such as IL-2, IL-6, and TNF-α [73].

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Once serotonin is released into the synaptic space, it activates the postsynaptic neuron and re-uptake by the presynaptic neuron. Both processes are regulated by the HT-1a receptors. High levels of serotonin in the synaptic space cause upregulation of the HT-1a receptors.

There are multiple hypotheses about how serotonin may influence CRF. The most straightforward hypothesis is that lower serotonin levels result in a decreased stimulation of the HT-1a receptors in the hypothalamus, and thereby in decreased activity of the HPA axis, resulting in lower cortisol levels [75]. A second hypothesis suggests that persisting high levels of serotonin or increased activity of the HT-1a receptors in the hypothalamus cause a change in the metabolism of the HPA axis, which leads to lower cortisol levels. This increased activity of the HT-1a receptors could be triggered by high levels of IL-1β and TNF-α [7, 58, 59]. The third theory, proposed by Jager et al., is that the relationship between serotonin levels and fatigue is U-shaped. This means that both a decrease and an increase in serotonin levels result in a lower cortisol level and fatigue [76].

Morrow et al. and Roscoe et al. have performed two randomized clinical trials using paroxetine, a selective serotonin reuptake inhibitor, in an effort to reduce fatigue during chemotherapy treatment [7, 8]. Both studies show improvement of depressive symptoms, but not of fatigue. These results suggest that correction of the serotonin level does not influence fatigue. This might be because downstream changes have already occurred at the moment patients start treatment, but one should realize that the evidence for the involvement of serotonin in CRF is only circumstantial.

Other Hormones

Other hormones that influence the activity of the HPA axis are androgens. Shafqat et al. showed that patients with cancer who have fatigue have lower levels of testosterone and dehydroepiandrosterone [77]. In patients treated with IFN, which causes fatigue in 70% of the patients treated, chronic inhibition of the HPA axis is seen, also resulting in lower levels of estrogen, progesterone, and testosterone. Treatment with IFN can also cause a decrease in growth hormone activity. All of these hormone deficiencies are associated with fatigue in otherwise healthy people, meaning that they also can contribute to CRF [78].

Cytokines

Both malignancy and its treatment are associated with a rise of cytokine levels in plasma [58, 59]. Pro-inflammatory cytokines like IL-1, IL-6, and TNF-α are found in the microenvironment of tumors [59, 60]. Wieseler-Frank et al. found that, in addition to tumor cells, glia cells within the central nerve system can also produce cytokines in response to stress [79]. These cytokines can contribute to CRF through their role in the development of anemia, cachexia, anorexia, and depression [59, 80], but also by the direct influence they have on the functioning of the HPA axis. In addition to aberrant expression, Collado-Hidalgo et al. and Bower et al. found three single nucleotide polymorphisms in the genes encoding IL-1β, IL-6, and TNF-α as a potential underlying mechanism of CRF in patients with severe fatigue after curative treatment for breast cancer [81, 82]. Bower et al. also showed that increasing numbers of high-expression alleles predict fatigue severity, which might explain some of the differences in fatigue levels among patients [82].

Treatment of CRF

Adequate treatment of CRF starts with identifying factors that contribute to the fatigue. A fatigue history should cover its severity, pattern, contributing and relieving factors, and the impact it has on daily functioning. Patients complaining of fatigue should also be assessed for depressive symptoms. Laboratory analysis can help diagnose or rule out anemia, electrolyte imbalance, and vitamin or hormonal deficiencies. The extent to which contributing factors are studied should be in line with the patient's current condition and prognosis.

The NCCN fatigue guidelines identify seven factors that may contribute to CRF. These factors are pain, emotional distress, sleep disturbance, anemia, nutritional deficiencies, decreased condition, and comorbidities [3]. All of these contributing factors influence the aforementioned pathophysiological mechanisms (e.g., pain causes serotonin release and nutritional deficiencies might hamper ATP regeneration). Anemia has been studied extensively as a treatable cause of fatigue in patients with cancer. The current standard is to treat these patients with red blood cell transfusion or with erythropoiesis-stimulating agents until the hemoglobin level is high enough to avoid transfusion [3]. There are, however, some

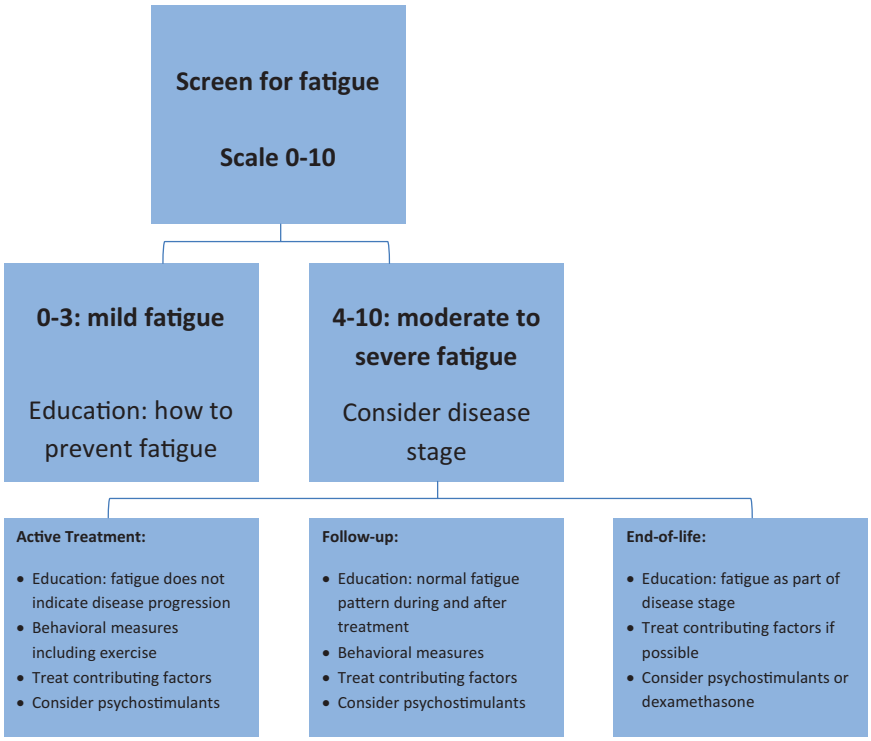

Figure 2. Summary of National Comprehensive Cancer Network guidelines. The National Comprehensive Cancer Network guidelines on cancer-related fatigue advises asking patients to rate their fatigue on a scale from 0 to 10 [3]. Suggested next steps are provided based on fatigue score and disease stage.

safety concerns about the use of erythropoiesis-stimulating agents in patients with cancer because they may increase the risk for thromboembolism [83]. Treatment of anemia may alleviate fatigue in the short term, but the study by Mercante et al. shows that this effect subsided at day 15 after transfusion, even though hemoglobin levels remained adequate [84].

In general, the specific cause of CRF is difficult to identify in a particular patient and its cause is expected to be multifactorial but primarily the result of the biological activity of the progressive disease and the severity of the treatment. Both pharmacological and nonpharmacological interventions can be applied to reduce CRF. A flow chart for treatment of CRF is provided by the NCCN and summarized in Figure 2 [3], but to date, there is little evidence that these interventions reduce CRF. Therefore, we believe that pharmacological interventions should be restricted because these interventions may lead to subsequent treatment-induced toxicity.

Nonpharmacological Treatment

Examples of nonpharmacological interventions in fatigue are patient education, fatigue diaries, sleep hygiene measures, cognitive behavioral therapy, and exercise [1, 3, 85–87]. Many patients try to reduce fatigue by resting, but this often does not restore energy and might even worsen fatigue in the long term [1, 88, 89]. Many practitioners advise sleep hygiene measures to patients with CRF. These measures focus on establishing a regular sleep pattern by performing activities during the day and avoidance of stimulants before and during the night [90–92]. Although these measures are often advised, there is little evidence for their efficacy [90–92].

Pro-inflammatory cytokines like IL-1, IL-6, and TNF-α are found in the microenvironment of tumors. Wieseler-Frank et al. found that, in addition to tumor cells, glia cells within the central nerve system can also produce cytokines in response to stress. These cytokines can contribute to CRF through their role in the development of anemia, cachexia, anorexia, and depression, but also by the direct influence they have on the functioning of the HPA axis.

Cognitive Behavioral Therapy

Another type of a nonpharmacological intervention is cognitive behavioral therapy. A systematic review performed in 2009 indicated that in four out of five randomized clinical trials, psychological interventions based on cognitive behavioral therapy specifically aimed at reducing fatigue were effective in reducing fatigue during cancer treatment [93]. In all of these randomized clinical trials, patients received education about fatigue, learned self-care or coping techniques, and learned how to balance activities and rest [93]. A critical note in this review is that follow-up measurements performed in these studies might indicate that the beneficial effect on fatigue subsides after the study intervention has ended.

Exercise

A number of trials have proven exercise as an effective nonpharmacological method to reduce fatigue in an outpatient setting [86, 94–100]. However, some of these trials are difficult to interpret because they lack proper randomization or placebo intervention [94]. Overall, Cramp et al. found a standardized mean difference of -0.27 (95% confidence interval: -0.37 to -0.17) in favor of exercise in their systematic review [98]. Currently, there is no clear evidence regarding what type

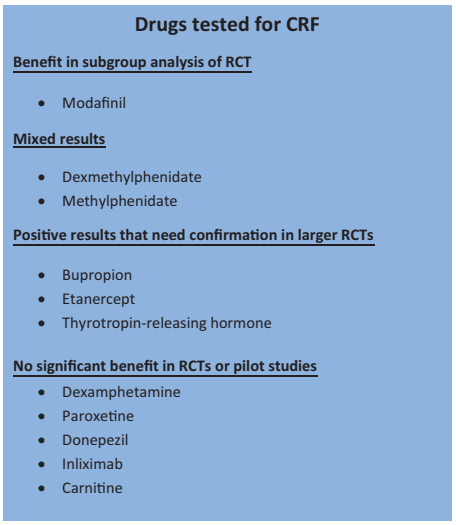

Figure 3. Drugs tested for cancer-related fatigue. This figure summarizes the results of the studies listed in supplemental appendix 2 into three categories: drugs showing no benefit over placebo; drugs showing a positive effect in small studies that need to be confirmed in larger, placebo-controlled trials; and one drug that showed some benefit over placebo in such a trial.

Abbreviations: CRF, cancer-related fatigue; RCT, randomized clinical trial.

of exercise is most effective, either low intensity, like walking, or high-intensity training [98]. In the PACES trial, which is currently ongoing, this question is addressed [101]. Most studies on exercise in those with cancer are performed in curative treatment settings. Although only a few small studies were conducted in patients receiving palliative care, and these also revealed reduced fatigue levels in the intervention group [85].

Pharmacological Treatment

Pharmacological treatment of primary CRF can have multiple entry points, such as reducing cytokine load by inhibition of the immune response, restoring peripheral energy depletion, and treating metabolic disorders [1, 102]. Anticancer treatment can alleviate fatigue by decreasing tumor burden, but it can also cause fatigue as a side effect. Most treatment options mentioned in palliative care guidelines are given to treat CRF symptoms, with for example, activating agents like dexamphetamine, (dex-)methylphenidate and modafinil.

To find pharmacological treatment options for CRF, a Medline search was performed. Details and results of this search can be found in supplemental online Appendix 2. Drugs that were studied for their effect on CRF were bupropion [103], (L-)carnitine [104, 118], dexamphetamine [105], dexmethylphenidate [106, 107], donepezil [108], etanercept [109], infliximab [110], methylphenidate [15, 111–115, 120], modafinil [2, 116], paroxetine [7, 8], and thyrotropin-releasing hormone [117]. Most drugs were not compared with placebo or did not show significant benefit compared with placebo (Fig. 3) [7, 8, 103–118]. One drug, methylphenidate, showed promising results [111–113, 119], but in the latest and largest trials, no improvement of fatigue by this treatment was found compared with placebo [114, 120, 121]. A variant of this drug, dexmethylphenidate, showed an improvement of fatigue compared with placebo in the trial by Lower et al., but there were also noticeable side effects [122]. In a subgroup analysis of one of the larger placebo-controlled trials, modafinil had significantly better effect on fatigue than placebo. This subgroup consisted of patients with severe fatigue at baseline (72.6% of the total study group) [2]. Effect size in this study that compared modafinil with placebo in 867 patients was small (-.50 points on a 10-point scale for modafinil, compared with -.33 for placebo in the whole group [$p = .08$] and -1.31 for modafinil compared with -0.87 for placebo in the severely fatigued patients [$p = .033$]). This might be partly because of the parallel start of treatment with chemotherapy.

Steroids such as dexamethasone and prednisone are often recommended in guidelines for CRF in the terminal stage [3]. This recommendation is based on clinical experience, supported by three studies in which fatigue was not an endpoint, but overall quality of life improved during treatment with steroids [123–125]. Until recently, no randomized controlled trial results were published on steroids with CRF as endpoint. The RCT performed by Yennurajalingam et al. showed positive effects of dexamethason on CRF compared to placebo [126].

Sleeping Agents

Sleeping agents are frequently used to treat patients with fatigue and insomnia. They often have adverse effects or even a paradoxical impact on sleep disturbance, especially in elderly patients, and are therefore not recommended for treatment of CRF [90, 127]. Melatonin agonists do not seem to have this adverse effect and can be considered as a sleeping agent for patients with insomnia, but they have not yet been evaluated for their specific effects on CRF [90]. Lissoni et al. have performed a number of trials to study the effects of melatonin on cancer progression and treatment side effects. They did find an effect of melatonin on fatigue as a treatment-related side effect, but a placebo effect cannot be ruled out [128–132].

Possible Future Interests for Pharmacological Treatment of CRF

Taking into account the likely role of cytokines in the pathophysiology of fatigue, drugs targeting excessive cytokine release, such as cyclo-oxygenase-2 inhibitors and nonsteroidal anti-inflammatory drugs, could be evaluated for their effect on CRF. In addition, α-melanocyte-stimulating hormone, a pituitary neuropeptide that functions as a mood-elevating substance and is known to inhibit certain pro-inflammatory activities of cytokines [133, 134], could be studied for its effect on CRF.

Complementary or Alternative Medicine

Chinese herbal medicine and other complementary therapies are frequently used by patients in addition to their normal treatment. Traditional Chinese medicine is often plant or herb based, sometimes complemented with minerals [135]. Although there are many articles applauding its effect, most of these studies have poor quality because of limited power, no comparison with placebo, or inadequate blinding. Among trials specifically studying the effects of complementary therapies on CRF, positive effects are found for bojungikki-tang, which consists of 10 different plant extracts, among which is a considerable amount of ginseng [136]. Barton et al., who studied different dose levels of American ginseng, did seem to find a dose-response relationship. However, the primary aim of the trial was not met, and results did not reach significance [137]. Another trial that studied the effects of ginseng had ma-

jor inclusion problems because of safety issues that can occur when ginseng is combined with other drugs [138].

Complementary therapies not only include oral treatments. Examples of other treatments are acupuncture and yoga. A review performed by Posadzki et al. showed inconclusive results for acupuncture trials, which were of variable quality [139]. This review did not include the study by Molassiotis et al., which showed positive results but could not rule out a placebo effect [140]. Yoga is increasingly practiced in Western countries and can be viewed as a type of low-intensity exercise. In a systematic review of the possible physical and psychosocial effects of yoga in patients with cancer, Buffart et al. found that yoga resulted in a moderate reduction of fatigue (Cohen's $d = -0.51$) but also mentions that the current evidence is insufficient to draw firm conclusions on the clinical implications [141].

For clinical practice, the lack of evidence regarding the effects of the different complementary therapies means that patient requests and questions about this subject should be handled with care while keeping in mind the possible interactions with other treatments.

Summary

CRF is a common problem for patients with cancer, both during and after treatment. It is disproportionate to physical activities, usually more severe than fatigue in healthy people, and has a negative influence on daily activities and quality of life. The EORTC QLQ-C30 fatigue subscale, the FACT-F, and the FQ are the most frequently used and best validated methods to assess CRF clinically. In the clinical setting, most patients are being asked to rate their fatigue on a scale from 0 to 10, with 4 or higher as a cut-off point to take further action [3].

Factors that may have a potential influence on CRF include physical and mental factors. With regard to the latter, changes in the levels of cortisol, serotonin, and several cytokines may have detrimental effects on the function of the hypothalamus and suprachiasmatic nucleus, possibly causing or increasing CRF.

Treatment of CRF starts with the identification and treatment of possible contributing factors such as anemia. When there are no solvable factors involved, symptomatic treatment should be applied. Currently, this consists mainly of supportive cognitive therapy and exercise programs, whereas pharmacological treatment should be avoided as much as possible because of the low success rate and potential toxicity. Modafinil is the only drug studied in CRF that showed a possible benefit over placebo in a subgroup of patients with severe fatigue before starting chemotherapy treatment.

In future studies of CRF, pharmacological agents to alleviate fatigue in patients receiving palliative care who cannot participate in exercise programs should be evaluated. Agents suggested for future studies are those that influence cytokine production, such as acetylsalicylic acid, because they show promising results in patients with other diseases who have fatigue.

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Disclosures

The authors indicated no financial relationships.

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